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Myelodysplastic Syndromes in Children. A Critical Review of the Clinical Manifestations and Management

Nicolas Novitzky[1]* and Gregor Prindull[2] for the European Society of Paediatric Haematology and Immunology (ESPHI) Myelodysplastic Syndromes (MDS) Working Party

[1]The University of Cape Town Leukemia Centre and the Department of Haematology, Groote Schuur Hospital, Observatory, Cape, Cape Town, South Africa

[2]Department of Paediatric Haematology and Oncology, The University of Göttingen, Göttingen, Germany

The FAB group has defined myelodysplasia in adults but direct application of this categorization to children has been controversial. Consequently, to outline the natural history of the disease better we have retrospectively analysed case reports and series published in English between 1982 and 1996. This study also included children with juvenile chronic myelomonocytic leukaemia (JCML) and monosomy 7 (Mo7). 340 patients were described in 27 publications. The mean presentation age was 5.91 (SD 5.04) years, and 34.9% were female. Constitutional alterations were described in 68 (20%) where refractory anemia (RA) and RA with excess of blasts (RAEB) predominated and were associated with a significantly longer survival. Among all patients progression to higher forms of MDS was noted in 61 (18%). Cytogenetic anomalies were detected in 59% of 227 children, and in 67 it was to Mo7. Amid those with Mo7, the clinical and laboratory characteristics as well as survival, closely followed their FAB type. Of the treatment options described, survival was significantly higher in those who underwent bone marrow transplant (BMT) (46.9%; $P = 0.00021$). Among children with JMML (CMML/JCML) not receiving a BMT, time to death was shortest in those best described as JCML (absence of constitutional and karyotypic derangement, thrombocytopenia and elevated Hb F). We conclude that children with constitutional abnormalities survive longer, Mo7 disorders are clinically and morphologically heterogeneous and should not be grouped into a single entity and that CMML and JCML may have biological differences. Finally, BMT remains the treatment of choice for those with primary MDS, as intensive chemotherapy is no better than supportive measures. Am. J. Hematol. 63:212–222, 2000.

Key words: pre-leukemia; constitutional disorders; monosomy of chromosome 7; Down's syndrome

INTRODUCTION

Myelodysplastic syndromes (MDS) represent a spectrum of clonal haematological ailments that have in common blood cytopenia, dysplasia and a predisposition to evolve into acute myeloid leukaemia (AML). The French American British (FAB) group attempted to understand the biology of these disorders through morphology [1], but later included cytogenetic and immunophenotypic characterization [2]. Since in those studies most patients were older, the understanding of the biology of these conditions is based upon observations made mainly on adults.

In children, these diseases are rare, accounting for around 3–9% of the hematological malignancies [3,4], although the real incidence may be unknown since in a proportion, morphology does not adhere strictly to the FAB criteria [6]. Furthermore, in children MDS appears

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*Correspondence to: Nicolas Novitzky, Dip. Med., Ph.D., Department of Hematology, University of Cape Town, Medical School, Anzio Road Observatory, 7925, Cape Town, South Africa. E-mail: novitzky@samiot.uct.ac.za.

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to run a more aggressive course and may be associated to familial or constitutional disorders [6,7] so that the pathobiology may be divergent to that in adults. Alternatively, in children, dysplasia with constitutional alterations and pre-leukemia (the type seen in adults) may be two different groups of diseases. Given these difficulties and in order to improve our understanding of these conditions, we have conducted an analysis of the clinical and laboratory features of children with MDS that were described in articles published from 1982, when the FAB classification became widely accepted.

PATIENTS AND METHODS

A retrospective review of manuscripts procured through MEDLINE (National Library of Medicine) was undertaken. Requirements were that these articles had been published in the English language between January 1982 and December 1996 on children with MDS aged 1 day to 16 years. Firstly, separate searches were prepared with the subjects: "pre-leukemia" or "myelodysplastic syndrome" leading to 2,282 publications and "child" or "pediatric" resulting in 387,171 articles. The combination led to 187 papers of children reported to suffer of MDS. From this group, only articles describing single cases or series containing demographic, clinical, and laboratory values that could be entered into a database were further scrutinized. Although one of the requirements was that the patients should reportedly be conforming to the FAB classification, those outlined as having juvenile chronic myelomonocytic leukemia (JCML) or monosomy of chromosome (Mo) 7 were incorporated as well. While there is agreement in the adult scientific literature that refractory anaemia (RA) with ringed sideroblasts (RARS) is a myelodysplastic disorder, this concept is less clear in pediatric patients. We were aware that in children this morphological diagnosis often correlated with a multisystem group of disorders that are associated with mitochondrial cytopathy and polyclonal haematopoiesis, but as they had been included in at least one major publication [6], we decided to incorporate these patients also into this series. One article did not report the diagnosis according the FAB criteria but provided sufficient data to include the 7 patients in the refractory anemia category (RA) [5].

The final diagnoses that were established by the authors were always accepted, as it was in instances where, although patients were morphologically described as having chronic myelomonocytic leukemia (CMML), they were catalogued by the authors as suffering from JCML. Separate analyses were then conducted comparing the outcome of these patients to the rest of the study population.

Abbreviations

AML	acute myeloid leukaemia
BMT	bone marrow transplantation
CMML	chronic myelomonocytic leukemia
FAB	French American British grouping
GVHD	graft-versus-host disease
JCML	juvenile chronic myelomonocytic leukaemia
MDS	myelodysplastic syndromes
Mo7	monosomy 7
IPSS	International Prognostic Scoring System
PA	refractory anemia
RAEB	refractory anemia with excessive blasts
RAEB-T	refractory anemia with excessive blasts transforming
RARS	refractory anemia ringed sideroblasts

Exclusions were known causes of secondary MDS, such as previous malignancies and their therapies, as well as those initially recovering from aplastic anemia. Similarly, because of the heterogeneous presentation of children suffering chromosomal breakage syndromes such as Fanconi's anemia or Bloom's syndrome, these disorders were also exempted. Furthermore, despite the possible association of leukemia (with/out therapy with G-CSF), due to the confounding effect of early mortality from infection children with congenital chronic neutropenia (Kostmann's syndrome) were also excluded. Lastly, articles were also exempted where patients' data were presented only as summary statistics ($N = 28$).

To establish the natural history of the disease, patients who had not undergone marrow transplants were analyzed independently, catalogued according to FAB, and their survival contrasted. Patients with JMML (JCML and CMML) and Mo7 were also segregated and their parameters studied separately.

Statistical analysis was undertaken employing a commercial package, where clinical and laboratory parameters of the whole population or the different FAB groups were scrutinised. Significance of subsets of patient characteristics was analyzed by *t*-test. Quantitative parameters in the various groups defined by Yates-adjusted Fisher's exact test. The survival of various sets of children with MDS was studied according to Kaplan and Meier and comparisons based on two-sided log-rank test. Prognostic factors for outcome were undertaken using the Cox regression analysis.

RESULTS

Of the articles that had been published between January 1982 and December 1996, 55 papers outlined children with myelodysplastic syndromes based on the FAB criteria [1]. However, in only 27 [4–30] were there adequate demographic, clinical, and laboratory data provided for their entry into a database and subsequent analysis. As a number of constitutional abnormalities had been described with MDS, to ensure their representation, separate searches for neurofibromatosis, Down's syndrome, Shwachman syndrome, Dubowitz syndrome, and

TABLE I. Clinical and Laboratory Characteristics Are Depicted in Children With MDS According to FAB Morphological Groups and in Those With JCML or Anomalies of Chromosome 7

Fab type (%) (*N*)	Age years (SD)	Gender F:M (*N*)	Constitutional abnorm (*N*)	Mean blood blasts (%)	Cytogenetic abnormal/ normal (*N*)	Alive: total (*N*)
All (100%)	5.91	119:221	68	2.89	133/94	115
($N = 340$)	(5.04)			(5.95)		
RA (25%)	6.82	33:52	24@	0.1		39
($N = 85$)	(5.47)			(0.39)@	30/24	
RARS (5%)	3.17	11:3*	5	0	1/6@	6
($N = 14$)	(4.2)					
RAEB (22%)	5.78	29:47	19^	1.04	38/17	20
($N = 76$)	(5.03)			(.71)		
RAEB-T (20%)	9.24	24:44	7	7.05	25/20	21
($N = 68$)	(4.65)#			(6.73)&		
CMML (23%)	3.24	20:59^	5	5.12	35/27	20
($N = 79$)	(3.42)$			(10.57)		
JCML (13.2%)	3.04	6:39#	6	13	8/22#	15
($N = 45$)	(1.46)^			(20.81)^		
IMo-7 (19%)	6.37	20:40	4$	8.22	N/A	16
($N = 67$)	(5.53)			(15.86)*		
$P =$	#6.82×10^{-7}	*0.001	@0.04	@6.3×10^{-6}	@0.006	
	1.08×10^{-5}	^0.039	^0.02	&0.002	#0.0013	
	^0.0002	#0.001	$0.007	^0.002		
				*0.003		

Patients with JCML and monosomy 7 were also included in the FAB groups and are displayed separately in the last 2 rows. Note that some of them had been included within the ones described in the FAB categories (for instance Mo7 or JCML and CMML). The bottom row describes the statistical significance of the differences ($P < 0.01$) in the values found in the various diagnostic subgroups in the column compared to the general patient population, and these different values are identified by the symbols $, ^, &, **, @, and #.

xanthogranuloma were conducted and again cross-referenced for MDS. Two further articles were retrieved [31,32], although since it was unclear which patients had also been reported in earlier publications [6,7], to avoid possible duplication, they were excluded. Similarly, papers with the text words "constitutional" or "somatic" abnormalities were also searched for but when combined with "myelodysplastic syndromes" and "pre-leukemia" no further publications fulfilled the inclusion criteria.

This led to the current report of 340 patients. Familial history of a related blood derangement was elicited in 19 children while in 68 cases, constitutional alterations were present (Tables I and II). It was assumed that the relevant clinical information was noted in all patients, as these publications often described in detail specific physical findings (somatic abnormalities). Organomegaly (hepatomegaly, splenomegaly, or both) were described in 136 patients and were absent in 88, while 21 had cutaneous infiltrates associated with MDS [33] in children. However, this information was not mentioned in 32 children presenting with JCML [13,16,22].

At the time of publication, with an overall mean follow up of 4.51 (median 3.6, SD 3.97) years, 225 had died or had been lost to follow-up ($N = 3$). Progression of the FAB diagnosis was noted in 80 and was higher to AML ($N = 61$; 76%) than to RA with excess of blasts (RAEB) ($N = 12$; 15%), or to RAEB in transformation (−T) ($N = 4$; 5%). In another 3 it was not specified, while spontaneous regression of the MDS was also observed in 2 children. The mean fetal haemoglobin blood concentration (Hb F) in 108 patients was 15.90 (median 8.3, SD 17.61) percent. Proportional hazard analysis showed that blood Hb F level ($\chi^2 = 5.37$; $P = 0.02$), platelet count ($\chi^2 = 15.22$; $P = 0.008$), and bone marrow transplantation (BMT) ($\chi^2 = 15.22$; $P = 0.0001$) were significant factors for survival.

Clinical Presentation According to FAB Groups

The morphological distribution according to the FAB criteria and other clinical and laboratory data for the study populations are shown in Table I.

Refractory anemia was diagnosed in 85 children. In one article [6], as suggested for adults [34], seven patients who did not have anemia, were also included. In 23, the hypoplastic variant of MDS was diagnosed [35]. Compared with the remaining FAB categories, familial ($N = 11$; $P = 0.001$) and constitutional abnormalities ($N = 24$; $P = 0.04$) were more prevalent in RA. Disease progressed to RAEB in 9, RAEB-T in 1 and to AML in 10. Patients with RA and ringed sideroblasts (RARS) were typically females ($P = 0.001$), while in 4, presentation was familial ($P = 0.01$), and in 5 children this morphological categorization was associated with mitochondrial cytopathy ($P = 5.25 \times 10^{-8}$). In two patients progression of the diagnosis was to RAEB, to RAEB-T in one and in another to AML.

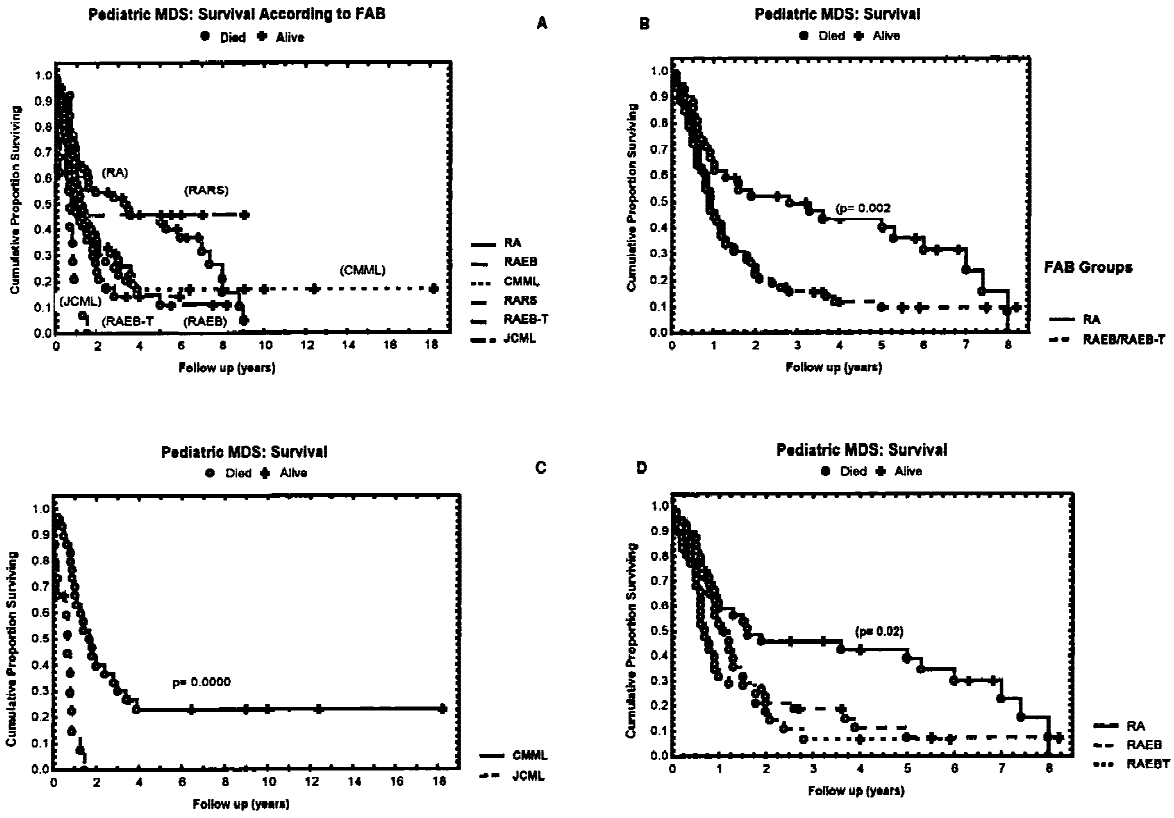

Fig. 1. Kaplan and Meier analysis of the survival of children with MDS (*N* = 242) according to FAB morphological groups (and including JCML). (A) Survival of all children. (B) Comparison of the survival of those with RA with those with excess of blasts in the marrow (RAEB/BAEBT). (C) Survival analysis of children with the diagnosis of JCML (*N* = 15) and CMML (*N* =30). (D)Survival of patients with RA and with excess of bone marrow blasts (RAEB or RAEBT) without constitutional abnormalities. None of these children were treated with myeloablative therapy and BMT.

In 76 patients, the diagnosis of RAEB was made on presentation, although in four, the bone marrow biopsy was hypocellular. Karyotypes were deranged in 69% and in 16 patients it involved chromosome 7. The disease progressed to RAEB-T and AML in two and 14 patients, respectively, but regressed spontaneously in one. Children with RAEB-T were significantly older at presentation. Karyotype was disturbed in 46% and was reported as Mo7 in 12. The disease transformed to AML in 21.

Children with CMML were the youngest, had a significantly higher incidence of organomegaly ($P = 1.0 \times 10^{-7}$), leukocytosis, and moderate cytopenias. Their mean blood Hb F level was 18.97 (SD 19.43), and 56% had abnormal karyotypes, with the most common cytogenetic aberration being again that of chromosome 7, which was detected in 18 ($P = 0.001$). In this FAB group, 24 were clinically described as JCML. In another 18 cases that were similarly defined as JCML, no FAB morphological diagnoses were included. Among patients with CMML 15 progressed to AML, although such evolution did not occur in any of those described as JCML.

Survival of all children not undergoing BMT and grouped according to FAB criteria is shown in Figure 1A–C. The mean survival of children with RA was significantly longer (mean 2.96 years; $P = 0.002$) when compared to those with RAEB/RAEB-T. Death occurred at a mean of 1.37 (median 0.9, 1.55) years from diagnosis. Those who died within 12 months of presentation tended to carry the diagnosis of JCML (Fig. 1C) or were significantly older (mean age 5.76 S.D. 4.9 vs. 2.45; SD 1.87; $P = 2.1 \times 10^{-7}$). Proportional hazard (Cox) regression analysis segregated the presence of constitutional abnormalities ($\chi^2 = 17.899$; $P = 0.00056$), transformation to higher type of MDS or leukemia ($\chi^2 = 5.943$; $P = 0.01$), elevated Hb F ($\chi^2 = 9.98$; $P = 0.001$), reduced platelet count ($\chi^2 = 4.79$; $P = 0.028$), and the diagnosis of JCML ($\chi^2 = 3.85$; $P = 0.04$) as independent factors significantly associated with survival. Of interest, when a subgroup of 117 children without somatic abnormalities (primary MDS) that had not received transplantation were separately analysed, similar findings were elicited. This analysis indicates a significantly longer survival

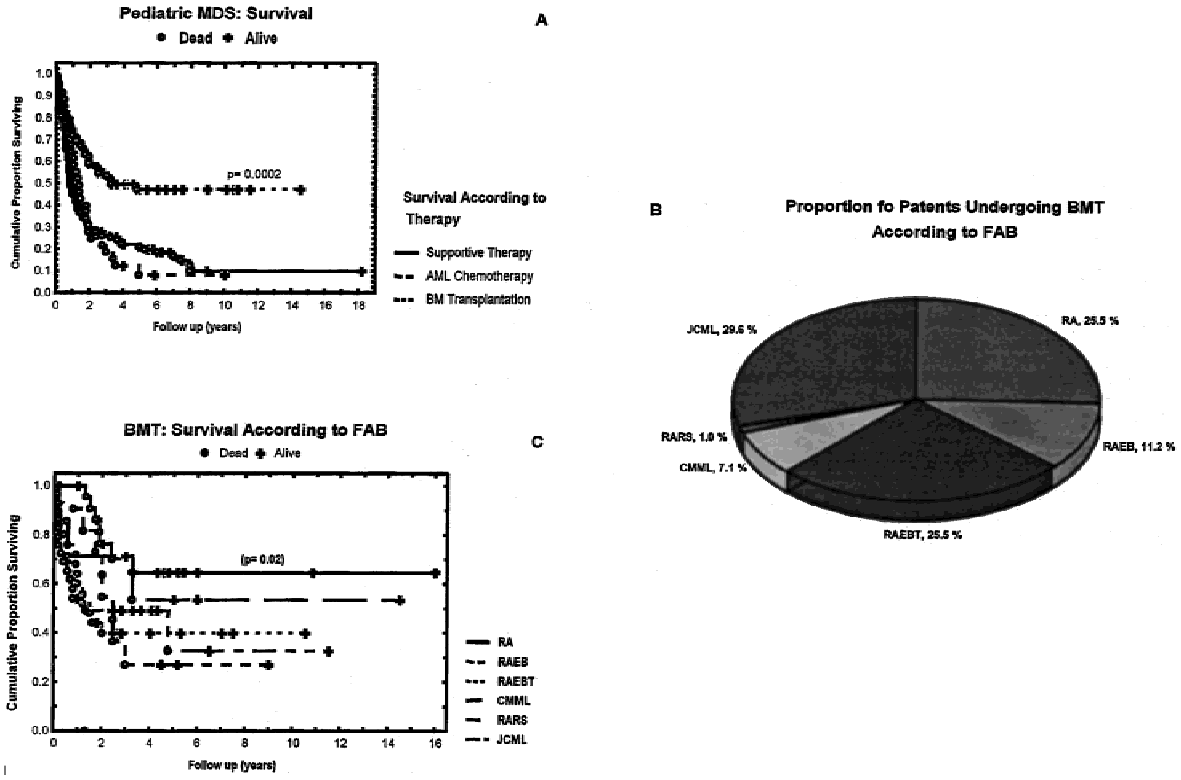

Fig. 2. Survival of children with MDS according to the 3 dominant therapies employed. (A) Comparison of bone marrow transplantation (BMT; *N* = 98), intensive chemotherapy (AML chemotherapy; *N* = 41), and supportive measures only (*N* = 135). (B) Pie chart representing the proportion of children undergoing BMT according to FAB morphological groups. (C) Outcome of patients receiving a BMT according to FAB groups and including JCML. One patient with RARS was transplanted but demised.

among RA compared to RAEB and RAEBT ($\chi^2 = 7.58$; $P = 0.02$; Fig. 1C) but not between these 2 latter groups (Fig. 1D).

Therapy of MDS in Children

The therapies instituted were bone marrow transplantation (BMT) in 98, cytotoxic schedules, similar to those prescribed in the induction therapy for acute myeloid leukemia, in 41, and the rest received a variety of supportive measures. Here, diverse approaches such as low-dose cytosine arabinoside ($N = 19$), oral etoposide ($N = 7$), splenectomy ($N = 4$), high-dose steroids ($N = 8$), or hematopoietic growth factors ($N = 3$) were tested. In 135 patients except for blood product transfusions, no other specific treatments were reported. In another 25 children no data on therapy was provided. Figure 2A shows that a significantly higher proportion survive following BMT (46.9%; $P = 0.00021$ log Rank).

Distribution and survival according to FAB or with JCML is depicted in Figure 2B and C. A significantly better outcome for those with RA is shown ($P = 0.02$). Constitutional anomalies were described in 13 patients, three of whom had a background of familial hematological abnormalities. Although numbers are low, it would appear that transplantation did not improve survival in this subgroup (Fig. 3C).

Data on the transplantation procedures were available in 55 patients. Bone marrow was derived from HLA identical siblings in 42 and matched unrelated donors in 13. The incidence of all forms of graft-versus-host disease (GVHD) was 41% but reportedly higher in those receiving grafts other than from HLA identical siblings (69%). Thirty-two percent relapsed to their original MDS and died. Thirty patients (46%) are alive and disease free at a mean follow-up of 2.74 years (SD 3.40). In 13 patients follow up was greater than 3 years, probably representing the patient population cured from the malignancy. None of the previously described clinical or laboratory parameters, pretherapy cytotoxic intensive schedules, type of preconditioning for BMT, nor the source of bone marrow for transplantation, was significantly associated with final outcome.

Somatic Abnormalities and MDS

In 68 patients myelodysplasia was part of congenital abnormalities, and 30 of them were surviving at the time

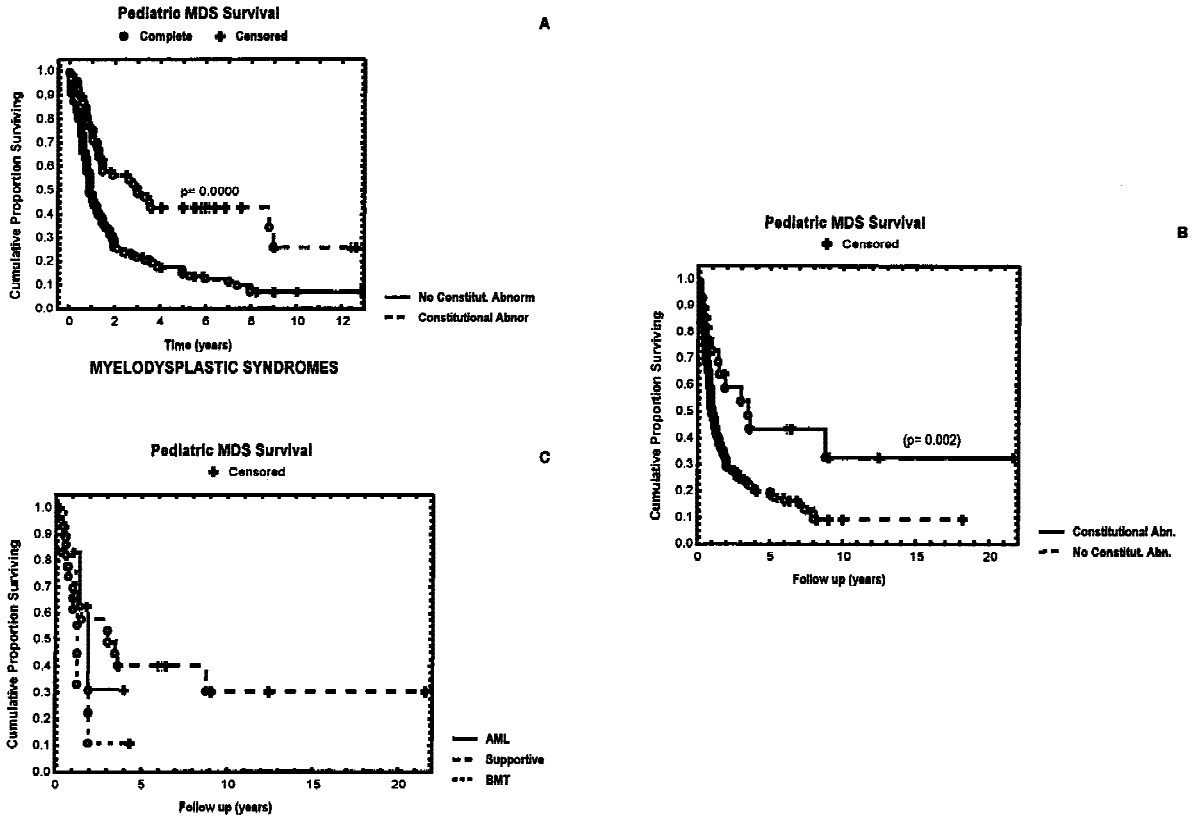

Fig. 3. Survival of children with MDS with (*N* = 69) and without congenital somatic abnormalities that were not treated with myeloablative therapy. (A) Survival of all patients with constitutional abnormalities is compared with those with primary MDS. (B) Survival of a corresponding population, but those with features of Down syndrome and RARS were excluded. (C) Outcome of these patients according to the therapies received (but including BMT).

of the reports. In 45, these were related to a specific constitutional syndromes such as Down's or Shwachman's syndromes (Table II), while in 23, blood abnormality was accompanied by other disorders with high prevalence of mental retardation and short stature. Down's syndrome was the most common affinity reported and significantly associated with the RAEB type ($N = 12$; $P = 0.00001$), while in 14, further cytogenetic abnormalities were also described (in 5, Mo 7). Among the remaining patients with constitutional abnormalities, the milder forms of MDS predominated, particularly RA (24; $P = 0.02$). Death related to progression of the disease to a higher FAB type was observed in 60/182 of patients with primary MDS (46 to AML) and 6 (5 to AML) in those with MDS and constitutional abnormalities ($P = 0.0016$), resulting in a significantly better survival ($P = 0.00001$ log Rank) (Fig. 3A). As MDS and acute leukemia in children with Down's syndrome have been reported to have a particularly favourable outcome [36] and death in RARS is rarely due to bone marrow failure, a separate analysis was conducted among those who did not receive a marrow graft, excluding these two groups. Survival of children with constitutional derangement (but disregarding Down's syndrome and RARS),

TABLE II. Patients With Constitutional Abnormalities According to Specific Syndromes and Other Somatic Derangement*

Constitutional abnormalities	*N*
Down's syndrome	22
Shwachman syndrome	5
Mitochondrial cytopathy and Pearson's syndrome	13
Neurofibromatosis I	3
Xanthogranuloma	2
Other somatic abnormalities	23
Mental retardation	(12)
Short stature	(7)
Total	68

*Figures in brackets quantitate the patients with other somatic findings within a group.

compared to those with primary MDS (without somatic abnormalities) were 50% and 21% ($P = 0.002$; log Rank), respectively (Fig. 3B). Proportional hazard analysis confirmed the independence of constitutional derangement as a significant factor for survival ($\chi^2 = 17.899$; $P = 0.00056$). Lastly, as therapeutic strategies, no survival differences were detected between BMT (mean 1.36 years, SD 1.13; $P = 0.67$) compared to sup-

TABLE III. Description of the Karyotypic Abnormalities Found in 227 Children With MDS Reported in Cytogenetic Studies*

Karyotype abnormality	*N*
Monosomy chromosome 7	67
(with other complex derangement)	(16)
Trisomy chromosome 8 (with other abnormalities)	9 (11)
Deletion chromosome 17	7
5q-	4
(with other abnormalities)	(2)
+21 (with other abnormalities)	(3)
Inversion 1	2
t(7;16)	2
Others	20
Total	114

*Children with trisomy of chromosome 21 associated with Down's syndrome were excluded. Figures in brackets describe the number of patients with other cytogenetic anomalies within a group.

portive measures (mean 3.58 years; SD 4.69) or intensive chemotherapy (mean 1.73 years; SD 1.25) (Fig. 3C).

Karyotypic Abnormalities

Cytogenetic derangement was reported in 59% of 227 children tested (Table III), and 48 of them were alive at publication (Fig. 4A). MDS was associated to isolated mental retardation in one and to Down's syndrome in another 22. In another 3, trisomy of chromosome 21 was part of an abnormal complex chromosomal aberration of bone marrow cells. Among patients with karyotypic abnormalities, disease progression was to AML in 30, to RAEB in 5 and additionally to RAEB-T in 1. After excluding children with Down's syndrome in those not undergoing transplantation, survival was not affected by the presence or type of karyotypic abnormality (Fig. 4A).

Monosomy 7 was the most common alteration, while in 16 patients additional complex aberrations were also reported. There were no significant differences in the FAB types between those with Mo7 and those with other clonal cytogenetic markers or those with normal karyotype. Forty-four patients with Mo7 did not receive a marrow graft. At the time of the reports, with a mean follow up of 2.41 (SD 2.72) years 12 progressed to AML, 3 to RAEB and 1 to RAEB-T and 34 (79%) had died. Survival favored the diagnosis of RA (Fig. 4B) but followed the FAB types. Seventy-two children were available for the analysis of the effect of BMT on karyotype. No significant differences in survival were elicited between those with normal or abnormal cytogenetic analysis, including monosomy of chromosome 7 (Fig. 4C).

Juvenile Chronic Myelomonocytic Leukemia (JMML): JCML vs. CMML

The diagnosis of JCML was accepted as stated in the publications regardless of FAB morphology. In many cases, the inclusion criteria for the diagnosis of JCML were neither offered nor discussed, except for providing some leading references. The FAB diagnosis was RA in 1, RAEB in 2 and CMML in 24 instances, in 18 children no morphological details were provided. For the analysis of the clinical and laboratory features, these children were then separated from the other FAB types (Table I).

To better discriminate the biological differences between JCML and CMML, all further analysis was undertaken only on children not receiving marrow transplants (16 and 60, respectively) and some differences were elicited. In general, children with JCML and CMML fell into similar age groups (mean age 2.63 SD 0.61 and 3.16 SD; 4.01; $P = 0.6$). Both were more common among boys and were characterized by organomegaly (15/16 and 38/45). However those with JCML had a significantly higher mean blood Hb F level of 28.4 (SD 15.71; $P = 0.0004$) percent and a lower prevalence of karyotypic abnormalities (3/14 vs 23/30; $P = 0.001$). Although these observations could have been the consequence of bias generated by disease definition, children with CMML had a significantly higher progression rate to AML ($N = 14$) than those with the diagnosis of JCML ($N = 0$; $P = 0.01$). Survival was significantly better in those with CMML (mean 3.31; SD 1.65 years; for JCML 0.59 SD 0.44 years; $P = 0.00001$ Cox-Mantel) (Fig. 1C).

Since considerable confusion has been originated with the described terminology and to resolve some of the above-mentioned discrepancies in the definitions, the term JMML has recently been proposed [38]. Ninety-seven patients fulfilled these characteristics, among which 62 that did not receive a marrow transplant were then combined in a new analysis. Outcome was significantly worse in those without constitutional abnormalities ($P = 0.0003$), higher Hb F ($P = 0.007$), blood blasts ($P = 0.05$), and more severe thrombocytopenia ($P = 0.04$) (Table V). Proportional hazard (Cox) regression analysis confirmed that absence of constitutional abnormalities ($\chi^2 = 7.05$; $P = 0.008$) and elevated Hb F ($\chi^2 = 5.17$; $P = 0.022$) remained as consistent indicators of poor outcome.

DISCUSSION

Myelodysplasia are a rare group of diseases of unknown aetiology. Although in some children the clinical behavior may correspond to the adult forms of presentation, it has been generally reported that the more aggressive types predominate [3,4]. In others, somatic dysmophism or other well-defined genetic alterations such as Down's syndrome and neurofibromatosis are associated with hematopoietic dysplasia, indicative of heterogenous pathobiologic mechanisms of hematopoieitic dysplasia. Furthermore, due to the limited understanding of the mechanism(s) of disease, no specific therapies are available.

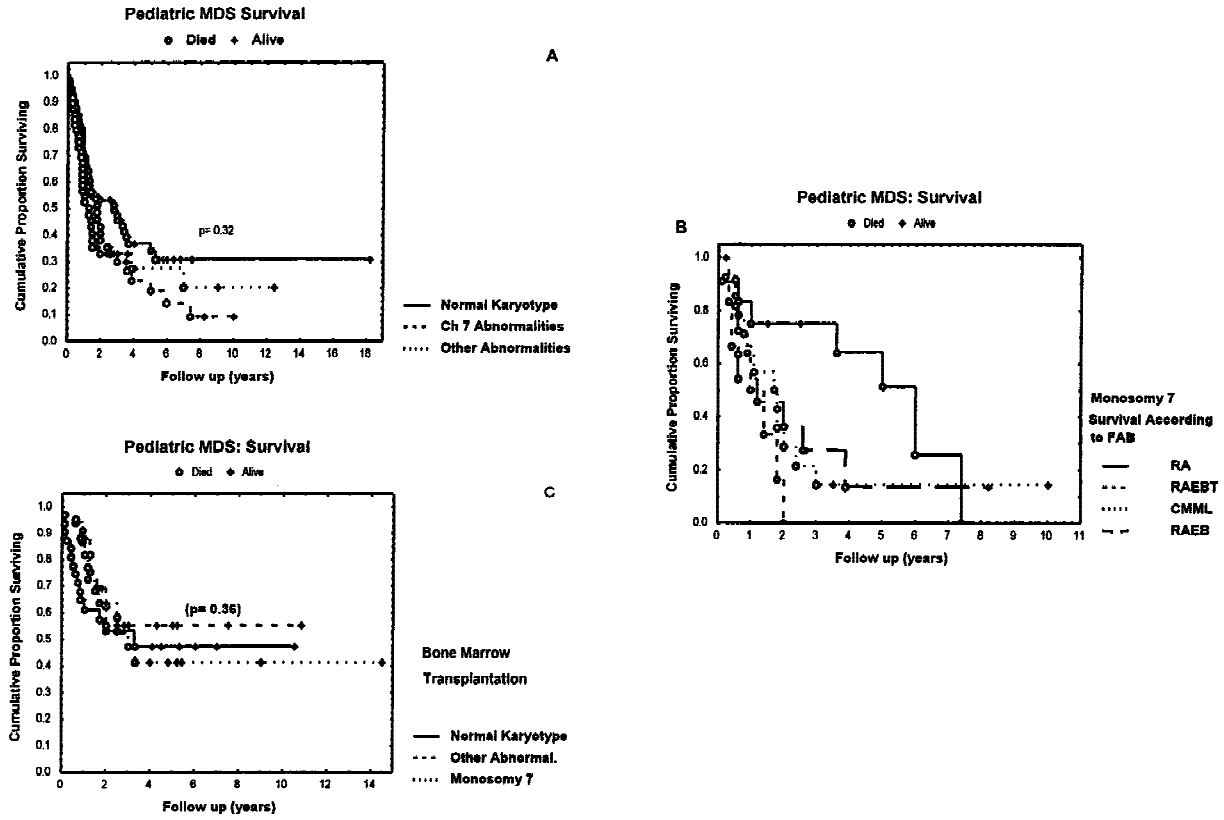

Fig. 4. Survival of children with MDS according to cytogenetic results. (A) Outcome according to normal karyotypes, monosomy 7, or other cytogenetic derangement. (B) Survival of patients with Mo7 according to FAB. (C) Outcome of BMT according to karyotype analysis.

TABLE IV. Clinical and Laboratory Features Associated With Poor Outcome for Patients With JMML Are Described*

JMML clinical and laboratory characteristics	Dead	Alive	*P*
Age	2.94 (3.21)	3.48 (5.14)	
Constitutional abnormalities:			
+	3/8	5/8	0.02
−	47/53	6/53	
HB F mean (SD)	18.3 (17.64)	3.35 (3.03)	0.007
HB mean (SD)	6.86 (2.41)	8.70 (3.26)	
WCC mean (SD)	46.21 (37.68)	23.03 (20.31)	0.07
Blood blasts mean (SD)	2.07 (3.45)	1.33 (1.52)	
Platelets mean (SD)	61.65 (62.44)	140.33 (55.59)	0.04
Bone marrow blasts mean (SD)	5.58 (5.94)	7.66 (4.61)	

*The significance in the differences between both groups is shown in the last column.

To our knowledge, this is the largest group of children with MDS collected in a single publication for such a retrospective review. However, with this kind of analysis several problems were evident. Firstly, although the morphological diagnoses were based on the FAB criteria [1], a considerable number of patients did not strictly fulfil the originally described types (neutropenia or thrombocytopenia without anemia, hypoplastic MDS) [34, 35]. This problem has also been the experience among adults, so that revisions to these recommendations have been published [34] that may have been followed in one of the series [6]. This may have resulted in a more selective reporting by others, favouring the more aggressive types of MDS. Lastly, considerable differences in opinion still exist with regards to the term JCML [3,7,33]. Although diagnostic criteria have even been proposed, the existence of this entity has been questioned by others who suggest that these patients represent a section within the spectrum of CMML as described by the FAB group.

Therefore, to avoid further confusion the new term JMML has recently been proposed [38,39]. Despite these constraints, this study was found to be valuable in several aspects. Firstly, it confirmed the marked heterogeneity of this group of disorders and the difficulties in using the FAB classification alone as a diagnostic or prognostic yardstick. Secondly, and divergent with the adult experience, together with RARS, patients with RA included a significantly higher proportion of children with associated familial hematological disorders and/or constitutional abnormalities (Table I). RARS was the least common of all groups, typically seen in girls with

constitutional abnormalities and while karyotypic anomalies were unusual (Table II) they also suffered early mortality (Fig. 1). However, sideroblastic anemia in children has been reported to be a genetic mitochondrial disorder, with polyclonal hematopoiesis that seldom progresses to leukaemia but rather terminate in multiorgan failure and therefore, it may be inappropriate to incorporate such patients among a series of children with MDS. Nevertheless, sideroblastic anemia in children has also been described in association with karyotypic abnormalities, suggesting that this disorder may include subgroups that might favor the progression to MDS [15]. Therefore, it may be argued that inclusion in this series of such patients among children with MDS, may assist in illustrating the differences with the adult variant and their research help clarify the different pathogenetic mechanisms that lead to ineffective hematopoiesis.

Thirdly, children with RAEB and particularly RAEB-T were older (Table I), had an aggressive disease with a high progression rate to AML with poor survival, and in many respects they behaved similarly to the adult variant of MDS. Although in adults FAB morphological classes associated with >20% bone marrow blasts were reported to experience shorter survival, in children this division did not provide for a significant discrimination from those with RAEB (Fig. 1B,D).

Fourthly, for the subgroup of patients with constitutional abnormalities, the more moderate FAB classes were prevalent, resulting in survival that was significantly longer than for those with primary MDS. Moreover, BMT as prescribed in these children appeared to be associated with early mortality and to offer no advantage to conventional chemotherapy or supportive management. Furthermore, although the number of patients is limited for a detailed analysis, in children with Down's syndrome, prolonged unsustained responses to intensive chemotherapy were also observed. This is consistent with a recent report on the outcome of children from two Children's Cancer Group trials suggesting that the biology of leukemia and MDS may be different in these patients [36]. When we conducted a separate analysis of the outcome of patients with somatic abnormalities but excluded both those with RARS and of Down's syndrome, Kaplan and Meier survival curves again confirmed that patients with primary MDS had significantly worse outcome (Fig. 3A,B). It remains unclear as to for the possible mechanisms for such a difference in survival that may include metabolic differences in the tumour or of the response to the treatment, as has been described in children with Down's syndrome [36,37].

In children, CMML evolved more like a hostile myeloproliferative disorder characterized by organomegaly, cutaneous infiltrates, and leukocytosis. In many aspects, their clinical features were consistent with the findings of a large series from Europe, including presentation age, number of blood leukocytes and platelets, incidence of karyotypic abnormalities, and poor prognosis given by thrombocytopenia and elevated Hb F levels [39]. Their therapy often included similar antineoplastic agents to those used for the management of myeloproliferative syndromes in adults (hydroxyurea, etoposide). We could not confirm that an age younger than 2 years had a protective effect on survival and except for one patient, all those not receiving a BMT ($N = 16$) died within 2 years of diagnosis (Fig. 1A,C and Table II). Patients reported to have JCML were distinguished from the CMML counterpart and the rest by a significantly higher blood Hb F and blast count (Table I), while cytogenetic abnormalities were reported infrequently. However, it is important to emphasize that there were no specific features that confirmed the diagnosis of JCML or excluded the pediatric type of CMML. Although the new terminology of juvenile myelomonocytic leukemia is inclusive of both groups [38] and this may imply a uniform outcome, our findings do not support this amalgamation in the nomenclature. Within this population, patients without constitutional abnormalities, thrombocytopenia and elevated blood Hb F (all characteristic features of JCML) were observed to have an adverse outcome (Table IV). In proportional hazard analysis, JCML diagnosis on presentation was also reaffirmed as a separate predictive factor for a poor outcome implying independent interactions from CMML.

The karyotype was abnormal in 59% of children with MDS. In multivariate and survival analysis cytogenetic abnormalities, including monosomy of chromosome 7, compared to those with normal karyotype, were not associated with unfavourable outcome (Fig. 4A). In a further examination of the data, we have separated children into the same cytogenetic subgroups that were found by the adult International Prognostic Scoring System to discriminate for survival [40]. These groups included good risk (normal or single −Y, (5q-) and del (20q)), poor risk (Mo7 and complex alterations), or intermediate risk (remaining cytogenetic abnormalities) karyotypes. Analysis failed to detect relation between karyotype and outcome (data not shown).

It was disappointing that intensive chemotherapy (without BMT) had not resulted in any benefit when compared to supportive measures only. Moreover, while BMT led to significantly superior long-term survival (46%; $P = 0.00001$), intensive cytotoxic treatment undertaken to induce a morphological response before BMT failed to provide any advantage. From these observations, it is suggested that allogeneic transplantation is the treatment of choice in primary myelodysplastic syndromes and that this therapy be offered as early as possible after diagnosis, as all the other approaches that have been described are ineffective.

Consequently, the challenge remains to explain why

such seemingly different entities as primary and several unrelated constitutional syndromes with associated MDS including mitochondrial MDS produce/give rise to cytomorpholgically similar forms of cellular dysplasia. Furthermore, we suggest that primary myelodysplasia be divided into only two patient groups that comprise those with ineffective hematopoieis (refractory cytopenias) and those with excess of blasts (>5% but <30%). Lastly those with CMML/JCML and RARS need better definition but should not be included within this group of myelodysplasia.

Nevertheless, due to the rarity of these conditions, only prospective studies, in the context of co-operative groups may be able to resolve these issues. Currently, The MDS working party from the European Society of Paediatrics Haematology and Immunology has undertaken such investigations in the hopes that the application of modern diagnostic techniques will enable them to realize these objectives.

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